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# Association of Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome and Evaluation of Role of Metformin in Reducing the Risk

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## 1. Introduction

### 1.1 Objective

To evaluate the prevalence of gestational diabetes mellitus (GDM) in women with polycystic ovary syndrome (PCOS) and to investigate the efficacy of Metformin in reduction of gestational diabetes in women with polycystic ovary syndrome.

### 1.2 Design

Review of literature on prevalence of gestational diabetes and evaluation of efficacy of Metformin in reducing the prevalence of gestational diabetes in women with polycystic ovary syndrome.

### 1.3 Setting

Reproductive Endocrinology section of Department of Obstetrics and Gynecology of Aga Khan University Hospital Karachi Pakistan.

### 1.4 Patient(s)

Women with PCOS and gestational diabetes

### 1.5 Intervention(s)

Literature search in the electronic databases MEDLINE, study of the references of all relevant trials or reviews, and manual search of the abstracts from the major meetings in the field of human reproduction.

### 1.6 Main outcome measure

Odds Ratio( OR) for the occurrence of gestational Diabetes.

### 1.7 Result(s)

Women with PCOS demonstrated a significantly higher risk for the development of GDM as compared with women without PCOS

### 1.8 Description

The Polycystic Ovarian Syndrome (PCOS) is a common endocrinopathy, affecting approximately 5–10% of women of reproductive age. In its classical form, the syndrome is characterized by oligo- or anovulation, biochemical or clinical hyperandrogenism and polycystic ovarian morphology on ultrasonography. Although much remains unknown regarding the underlying pathophysiology of PCOS, a form of insulin resistance intrinsic to the syndrome appears to play a central role in its development. Among many women with PCOS, the observed insulin resistance is partially explained by excess adiposity; however, it is increasingly recognized that even lean women with PCOS have increased insulin resistance compared with normal controls. Affected women have an increased risk of glucose intolerance, gestational diabetes mellitus (GDM) and type 2 diabetes. Some studies suggest the risk of GDM is higher among PCOS versus non-PCOS women, and several studies note an increased prevalence of polycystic ovarian morphology and symptoms in women with prior GDM.

Insulin resistance is defined as the decreased ability of insulin to stimulate glucose disposal into target tissues, or a reduced glucose response to a given amount of insulin. Chronic hyperinsulinemia is a compensatory response to this target tissue resistance. Several mechanisms have been suggested to explain insulin resistance, including peripheral target tissue resistance, decreased hepatic clearance, or increased pancreatic sensitivity. The peripheral insulin resistance in PCOS is uniquely due to a defect beyond the activation of the receptor kinase, namely, reduced tyrosine autophosphorylation of the insulin receptor and enhances the expression of hyperandrogenism by its inhibitory effect on hepatic sex hormone binding globulin (SHBG) production thereby increasing the bioavailability of androgens which leads to metabolic and obstetrical complications. Significant metabolic burden of insulin resistance is seen in women with PCOS, affected women may have an increased risk of impaired glucose tolerance (IGT), GDM and type 2 diabetes mellitus (DM).

In pregnant women with PCOS, the increasing tissue resistance to insulin, mainly caused by placental hormones, adds on the preexisting state of insulin resistance, which may accompany the syndrome. This pathogenic mechanism could lead to hyperglycemia, reflected in a higher incidence of GDM. However, studies on GDM prevalence in women with PCOS gave conflicting results; considering the heterogeneity of PCOS and the diversity in methodology of screening and diagnosing GDM, these results should have been expected.

A method of combining the results of the studies addressing the risk of Incidence of GDM in women with PCOS was one of the endpoints in addressing pregnancy complications in women with PCOS. Women with PCOS demonstrated a significantly higher chance of the development of GDM, though with significant statistical heterogeneity among the studies. This heterogeneity was not further analyzed or accounted for. To examine whether women with PCOS have a greater risk for the development of GDM than women without PCOS, we performed a review of literature and analysis of available trial

## 2. PCOS, Gestational Diabetes Mellitus (GDM) and diabetes

It has been recognized that women with PCOS have a higher risk for developing type 2 diabetes mellitus and gestational diabetes. In a retrospective cohort follow-up of patients with PCOS, the prevalence of diabetes mellitus was 7-fold higher than in controls.

Gestational diabetes is defined as impaired glucose tolerance diagnosed for the first time during pregnancy, occurs in 2–5% of pregnancies and usually resolves at the end of gestation. However, between one half and one third of women with gestational diabetes may develop diabetes 2–11 years post-partum. Different studies have shown that women with PCOS have a higher risk for the development of gestational diabetes in relation to insulin resistance. Moreover, other authors have demonstrated a high incidence of polycystic ovaries in women with history of gestational diabetes. Gestational diabetes is associated with a high neonatal morbidity and given that patients with PCOS have a high prevalence of gestational diabetes, these women should be considered to be at risk. Therefore, preventive measures before pregnancy to minimize neonatal morbidity should be recommended, including dietary advice and physical exercise as well as to indicate insulin-sensitizing treatments before; and during pregnancy.

In reproductive age, the prevalence of type 2 diabetes mellitus is estimated between 1.7 and 6.1%. This prevalence would be expected to be from 5–10-fold higher in women with PCOS. On the other hand, PCOS may be considered a pre-diabetic state with a prevalence of impaired glucose tolerance of 31–35% and a prevalence of type 2 diabetes of 7.5–10%. Impaired glucose tolerance is characterized by moderate increases of fasting glucose levels that may precede diabetes. Women with impaired glucose tolerance are asymptomatic; therefore, an oral glucose tolerance test is required for diagnosis. Conversion of impaired glucose tolerance to frank diabetes in women with PCOS is 5–10 times more frequent compared with normal women. The mean age at diagnosis of type 2 diabetes mellitus in patients with PCOS (30–40 years of age) is lower than in normal women (60–70 years of age). Additionally, a family history of diabetes and the presence of obesity are important predictors for the development of type 2 diabetes mellitus.

The diagnostic criteria of diabetes based on the 1999 World Health Organization definition and the 1997 recommendations of the Expert Committee of the ADA is a fasting glucose level  $\geq 126\text{mg/dl}$  ( $7\text{mmol/l}$ ) or oral glucose tolerance test (2h plasma glucose after 75g oral glucose challenge)  $\geq 200\text{mg/dl}$  ( $11.1\text{mmol/l}$ ). Diagnostic criteria of impaired glucose tolerance include normal fasting glucose levels ( $<126\text{mg/dl}$ ) in association with oral glucose tolerance test  $\geq 140$  and  $<200\text{mg/dl}$  ( $7.8\text{--}11.1\text{mmol/l}$ ). Normal baseline plasma glucose levels are  $110\text{mg/dl}$  ( $6.1\text{mmol/l}$ ). The principal difference between the 1997 ADA criteria and the 1999 WHO criteria is that the ADA criteria discourage the use of the oral glucose tolerance test as a routine diagnostic tool whereas the WHO criteria do not. However, it seems that the WHO criteria are more adequate for the diagnosis of diabetes in women with PCOS tolerance test.

These data indicate that women with PCOS are at high risk for long-term development of type 2 diabetes mellitus, and support the importance of an early diagnosis and treatment of insulin resistance to help reduce the incidence and severity of diabetes, dyslipidemia, hypertension and cardiovascular disease.

3. Review of role of insulin sensitizing agents (metformin) in prevention of gestational diabetes in women with pcos

A major change in the treatment of PCOS was initiated by the understanding that many women with this disorder compensate insulin resistance with a period of hyper secretion of insulin by the pancreatic beta cell. This understanding has been incorporated into the framework of PCOS treatments through the beneficial effects of insulin-sensitizing treatments on the PCOS phenotype Agents that improve insulin sensitivity (and lower circulating insulin levels) include metformin as well as thiazolidinediones, pioglitazone and rosiglitazone as alternative pharmacotherapies for those who cannot tolerate metformin as a result of gastrointestinal side effects .These treatments have resulted in beneficial changes in PCOS phenotype with increased menstrual and ovulatory frequency, pregnancy and decreased hirsutism. On the other hand, an increase in obstetrical pathology in women with PCOS has been documented, including increased rates of miscarriage, gestational diabetes, macrosomia, caesarean deliveries and pre-eclampsia. Given that hyperinsulinaemia may play a role in the pathophysiology of these conditions, maintenance of oral antidiabetic agents during pregnancy may decrease the incidence of these complications. Metformin, with a high safety profile for use during pregnancy, has been given to pregnant women with PCOS resulting in a reduction of the aforementioned conditions in these patients.

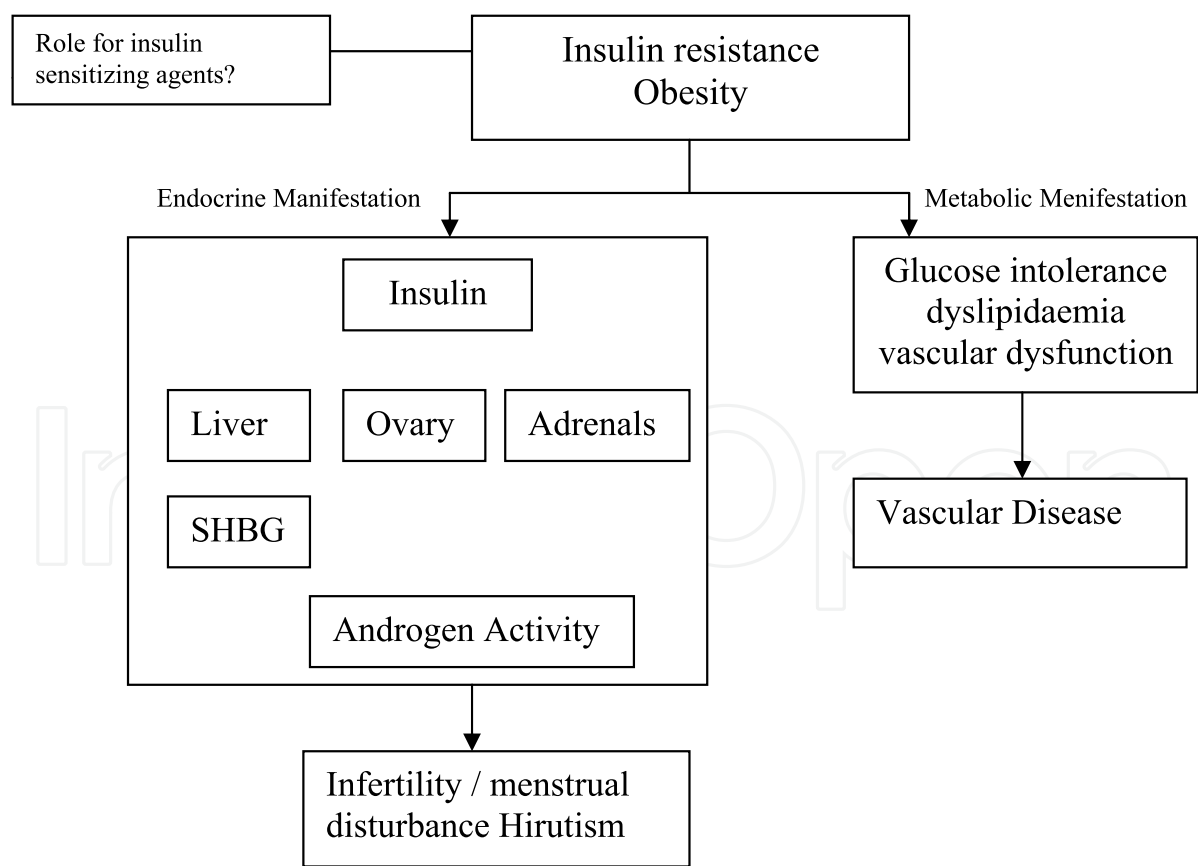


Fig. 1. Postulated role for insulin sensitizing agents on target tissues affected in woman with PCOS Harborne L etal

These concepts have quickly become the cornerstone of diagnosis and treatment of PCOS and other diseases also associated with insulin resistance. Type 2 diabetes mellitus and gestational diabetes. Recent observations regarding the effect of insulin-sensitizing drugs on ovarian stimulation in patients with PCOS undergoing IVF are also discussed, as well as the current status of the use of insulin-sensitizing drugs during pregnancy. Finally, substantial progress has been made to elucidate the cellular and molecular mechanisms of insulin resistance in PCOS. The insulin receptor and genetics of PCOS are complex areas that are extensively being investigated.

These agents increase the tissue sensitivity to insulin action in vivo. The agent commonly used in clinical practice is metformin, an oral hypoglycemic biguanide. Newer agents include the thiazolidinediones group of drugs like troglitazone. Hepatotoxicity of this drug has led to its withdrawal, but pioglitazone and D-chiroinositol has been used with some success in an insulin sensitization in women with PCOS

### 3.1 Metformin

It acts primarily by increasing peripheral glucose uptake in response to insulin at post receptor level, with some basal reduction in gluconeogenesis. It improves the insulin sensitivity in adipose tissues and skeletal muscles. All of the action are mediated by CAMP activated by protein kinase. It has been suggested that various insulin sensitizing drugs specifically inhibits the 17, 20 lyase activity of P450c 17. While it true that these drugs lower the C19 steroids but still the exact mechanism of action of metformin is not clear.

Until now the use of insulin sensitizing agents are targeted toward symptoms and signs of PCOS, like in ovulation induction, as an anti androgen therapy and for hirsutism. In this chapter we will be discussing the role of insulin sensitizers particularly metformin in prevention of Gestational diabetes associated with PCOS in light of recent evidence support.

### 3.2 Use of metformin and prevention and treatment of gestational diabetes mellitus

Metformin has been used to treat diabetes in second and third trimesters of pregnancy after the main teratogenic period, no significant perinatal morbidity and mortality was noticed except relatively high frequency of neonatal jaundice. Coetzee *et al.*<sup>14</sup>, has published the experience of 118 pregnant women with PCOS, who received an oral hypoglycemic medication and found the higher frequency of preeclampsia and perinatal mortality. However when these study results were critically analyzed it was found these women were older, more obese than their reference group which accounted for the baseline characteristics rather than Metformin alone.

The incidence of gestational diabetes in women with PCOS appears to be increased but data are not consistent. Insulin resistance in PCOS and the inability of pancreatic beta cells to compensate for increased needs of insulin during pregnancy are risk factors for gestational diabetes.

Different studies have documented a decrease in the incidence of gestational diabetes in PCOS women treated with metformin during pregnancy. Although in most of them retrospective controls were used. Prospective randomized studies with a sufficient number of patients are necessary in order to provide good evidence to recommend the use of metformin during pregnancy.



#### 4. Conclusion

PCOS is one of the most common hormonal disorder affecting women and has reproductive, metabolic, cardiovascular health implications across the life span. Insulin resistance in PCOS has been considered as main etiological factor for major health related consequences. Significant heterogeneity among studies and dependence of the outcome on study type make the higher risk of GDM in women with PCOS a questionable finding. The conduction of properly designed studies should precede any recommendation to pregnant women with PCOS in regard to the risk of GDM.

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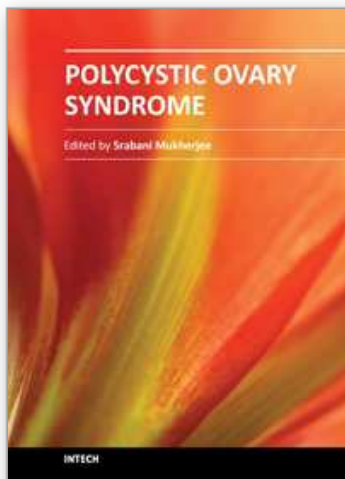
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## **Polycystic Ovary Syndrome**

Edited by Dr. Srabani Mukherjee

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Brought into the limelight many decades ago, Polycystic Ovary Syndrome (PCOS) is still, to date, surrounded by controversy and mystery. Much attention has been attracted to various topics associated with PCOS research and there has been a healthy advance towards bettering the understanding of the many implications of this complex syndrome. A variety of topics have been dealt with by a panel of authors and compiled in this book. They span methods of diagnosis, reproductive anomalies, metabolic consequences, psychological mindset and ameliorative effects of various lifestyle and medical management options. These books are designed to update all associated professionals on the recent developments in this fast-growing field and to encourage further research into this thought-provoking subject.

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